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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,060	10/07/2003	Christopher D. Gocke	97,078-P	8294

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EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	**Application No.** 10/680,060	**Applicant(s)** GOCKE ET AL.
	Examiner Suryaprabha Chunduru	**Art Unit** 1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response to the office action filed on September 8, 2006 has been entered.

Status of the Application

2. Claims 1-33 are pending. Applicants' arguments are fully considered and found persuasive in part for the reasons that follow. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. This action is made Non-final.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A. Claims 1-4, 6, 8, 10-11, 13-18, 20-22, 24-28, 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sorenson (WO 93/22456).

Sorenson teaches a method of claim 1 and 26-27, 33 for determining an acquired predictive risk for a non-hematological disease in a human without cancer having adenoma, or with adenoma cancer wherein the method comprises

(a) purifying extracellular nucleic acid (soluble DNA) from blood (blood plasma) from a human subject (with cancer and without cancer) to prepare extracted extracellular nucleic acid containing DNA encoding a mutated gene (K-ras oncogene) (see page 7, paragraph 2 under the sub-title detailed description of the invention, page 8, paragraphs 1-2, page 12, paragraph 1, page 25, line 1-6 indicating use of normal DNA sample and tumor DNA sample);

(b) enriching the extracted extracellular nucleic acid for the mutated DNA, wherein the mutated DNA is concentrated or isolated from the remaining extracted extracellular nucleic acid (see page 7, paragraph 2, page 9, paragraph 1, indicating enriching the extracted DNA using a solid support with attached anti histone antibodies);

(c) amplifying the mutated gene DNA from the enriched mutated DNA (see page 7, paragraph 2, page 9, paragraph 2, page 12, paragraphs 1-2);

(d) detecting the amplified mutated DNA , whereby the detection of amplified product determines the presence of mutant tumor DNA in a said samples (see page 7, paragraph 1 under subtitle detailed description of the invention, page 8, line 1-6, page 12, paragraph 1, page 37, claim 1);

With regard to claim 2, 32, Sorenson teaches that the amplified product is detected using gel electrophoresis (see page 41, claim 19, page 20, paragraph 1, page 23, line 23-26).

With regard to claim 3, 17, 28, Sorenson teaches that the extracellular nucleic acid is from plasma or serum fraction of blood (see page 42, claim 20, page 8, paragraph 1).

With regard to claim 4, 31, Sorenson teaches that the amplification is carried out using polymerase chain reaction, ligase chain reaction (see page 38, line 1-10).

With regard to claims 10-11, 13, 21-22, 24-25, 30, Sorenson teaches that the mutated oncogene is K-ras , p53, associated with microsatellite marker (see page 40, claim 16, page 12, paragraph 1, page 23, paragraph 1, page 20, paragraph 1, page 21, paragraph 1).

With regard to claim 8, 20, Sorenson teaches that the hybridized complex is separated using electric field (gel electrophoresis) (see page 23, paragraph 1).

With regard to claim 14, Sorenson teaches that the non-hematologic disease is a colorectal adenoma (adenocarcinoma of colon) (see page 12, paragraph 1).

With regard to claim 15, Sorenson teaches that the mutated gene is absent in normal cells from the human (see page 12, line 1-6, page 20, paragraph 1).

With regard to claims 6, 16, Sorenson teaches that the enriching purified DNA comprises hybridizing an oligonucleotide probe to the mutated DNA and separating the hybridized product from non-hybridized nucleic acid thereby enriching the purified DNA (see page 23, paragraph 1).

With regard to claim 18, Sorenson teaches that the oligonucleotide is further bound to non-biological surface (solid support) (see page 24, paragraph 1, indicating the biotinylated oligonucleotide is captured on a avidin or streptavidin attached support).

Although Sorenson teach detection of mutant circulating tumor DNA in individuals with and without cancer, Sorenson et al. did not specifically teach the presence of said mutant DNA is a predictive risk factor for a non-hematologic disease in a human without cancer. However, it would have been prima-facie obvious to one skilled in the art to modify the teachings of

Sorenson to achieve an expected advantage of developing a method for determining an association of the presence of said mutant DNA as a predictive risk factor for a non-hematologic disease in a human without cancer, because Sorenson explicitly taught the detection of mutant DNA could be used as a diagnostic marker for detecting various types of cancer, because the levels of circulating soluble DNA are significantly increased (20-fold excess) in cancers including non-hematological diseases such as adenocarcinomas and suggest the the method can be used to detect certain cancers and other diseases which tend to increase levels of circulating soluble DNA (see page 2, paragraphs 1-3, page 3, paragraph 1 under Summary of invention, page 4, paragraph 1). An ordinary practitioner would have a reasonable expectation of success that the modification of the method taught by Sorenson would resulting predicting the occurrence of a non-hematologic disease in human without cancer because Sorenson explicitly taught the increased levels of said mutant DNA is a diagnostic marker for detecting cancers including adenocarinomas and such modification is considered obvious over the cited prior art.

B. Claims 5, 9 rejected under 35 U.S.C. 103(a) as being unpatentable over Sorenson et al. (WO 93/22456) as applied to claims 1-4, 6, 8, 10-11, 13-18, 20-22, 24-28, 30-33 above, and further in view of Ronai (US 5,512,441).

Sorenson teaches a method for determining an acquired predictive risk for a non-hematological disease in a human without cancer having adenoma, or with adenoma cancer as discussed above in 3A.

However, Sorenson did not specifically teach the use of endonuclease-mediated restriction digestion.

Ronai teaches a method for detecting Ras oncocogene in human samples, wherein the method comprises, enriching mutated ras gene using restriction endonucleases (see col. 3, line 13-28). Ronai et al. also tech that said restriction endonuclease comprises BstN1 (see col. 3, line 13-28).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the method for detecting extracellular nucleic acid encoding a mutated gene in a sample as disclosed by Sorensen with a step of endonuclease-mediated digestion as taught by Ronai for the purpose of enriching mutated gene fragments for sensitive detection. An ordinary artisan would have a reasonable expectation of success that inclusion of the step of endonuclease-mediated digestion would result in enriching mutated gene as taught by Ronai because Ronai explicitly taught that the enrichment of mutated ras gene using endonuclease BstN1 would improve the detection of mutation in ras gene by reducing the background wild type sequences that are cleaved by said endonuclease (see page 2, line 52-67, col. 3, line 1-12) and such modification of the method would be obvious over the cited prior art.

C. Claims 7, 19, rejected under 35 U.S.C. 103(a) as being unpatentable over Sorenson et al. (WO 93/22456) as applied to claims 1-4, 6, 8, 10-11, 13-18, 20-22, 24-28, 30-33 above, and further in view of Breivik et al. (WO 95/13368).

Sorenson teaches a method for determining an acquired predictive risk for a non-hematological disease in a human without cancer having adenoma, or with adenoma cancer as discussed above in 3A.

However, Sorenson did not specifically teach the use of magnetic field to separate hybridized complex.

Breivik et al. teach a method for isolation of nucleic acid using a solid support to capture DNA, wherein the solid supports include magnetic particles, which provide advantage of a quick, simple and efficient way of separating the particles following capture of DNA on to the particles, that avoids traditional centrifugation which generates shear forces that degrade nucleic acids (see page 7, paragraphs 4-5).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the method for detecting extracellular nucleic acid encoding a mutated gene in a sample as disclosed by Sorensen with a step of using a magnetic field as taught by Breivik et al. for the purpose of enriching mutated gene fragments for sensitive detection. An ordinary artisan would have a reasonable expectation of success that inclusion of the step of use of magnetic particles and separation of captured DNA on the particles using a magnetic field would result in enriching mutated gene because Breivik explicitly taught that the use of magnetic particles would provide advantage of a quick, simple and efficient way of separating the particles following capture of DNA on to the particles, that avoids traditional centrifugation which generates shear forces that degrade nucleic acids (see page 7, paragraphs 4-5) and such modification of the method would be obvious over the cited prior art.

D. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sorenson et al. (WO 93/22456) as applied to claims 1-4, 6, 8, 10-11, 13-18, 20-22, 24-28, 30-33 above, and further in view of Moran et al. (Canadian Med. Assoc. J., Vol. 150 (10) pp. 1544, 1994).

Sorenson teaches a method for determining an acquired predictive risk for a non-hematological disease in a human without cancer having adenoma, or with adenoma cancer as discussed above in section 3A.

However, Sorenson did not specifically teach the use of sigmoidoscopy.

Moran et al. teach a method for diagnosis of colorectal cancer using sigmoidoscopy for detecting colorectal adenomas (see page 1544, col. 1-2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of detecting a mutated gene in screening for adenoma of colon as taught by Sorenson et al. with a diagnostic procedure using sigmoidoscopy to detect colorectal cancer as taught by Moran et al. for the purpose of developing a sensitive method for diagnosing a colorectal cancer. An ordinary artisan would have a reasonable expectation of success that inclusion of the step of using sigmoidoscopy would result in developing a sensitive and accurate method for diagnosing adenoma in a human subject because Moran et al. explicitly taught that the use of flexible sigmoidoscopy for screening patients for colorectal disease would reduce the rate of death from rectal cancer (see page 1544, col. 1-2) and such modification of the method would be obvious over the cited prior art.

E. Claims 12, 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sorenson et al. (WO 93/22456) as applied to claims 1-4, 6, 8, 10-11, 13-18, 20-22, 24-28, 30-33 above, and further in view of Albertsen et al. (US 5,648,212).

Sorenson teaches a method for determining an acquired predictive risk for a non-hematological disease in a human without cancer having adenoma, or with adenoma cancer as discussed above in section 3A.

However, Sorenson did not specifically teach the mutated gene as APC.

Albertsen et al. teach a method for detecting APC gene mutations in colorectal cancer patients and also disclosed that the significance of detection of mutations in APC would be correlated to the occurrence of familial or sporadic colorectal adenoma (see col. 3, line 17-23, line 60-67, col. 4, line 1-3)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of detecting a mutated gene in screening for adenoma of colon as taught by Sorenson et al. with APC gene mutation detection in high risk colorectal cancer patients as taught by Albertsen et al. for the purpose of developing a sensitive method for diagnosing a colorectal cancer. An ordinary artisan would have a reasonable expectation of success that inclusion of the step of detecting APC gene mutations would result in developing a sensitive and accurate method for diagnosing adenoma in a human subject because Albertsen. et al. explicitly taught that the detection of APC gene mutations and their association with occurrence of the colorectal disorders (see col. 3, line 60-67, col. 4, line 1-3) and such modification of the method would be obvious over the cited prior art.

Response to arguments:

4. With regard to the objection to the informalities, Applicants' arguments and amendment are fully considered and the objection is withdrawn herein in view of the amendment.

5. With regard to the objection to the abstract of the disclosure, Applicants' arguments and amendment are fully considered and the objection is withdrawn herein in view of the amendment.

6. With regard to the rejection of claims 1-4, 6, 8, 10-11, 13-18, 20-22, 24-28, 30-33 under 35 U.S.C. 102(b) as being anticipated by Sorenson (WO 93/22456). Applicants' arguments are fully considered and are found persuasive in part. Applicants' argue that Sorenson does not teach detecting a mutant allele without cancer. The rejection is withdrawn herein, however, Sorenson

reference does suggest that the detection of mutant gene in normal individuals and presence of said mutant gene could be used as a diagnostic marker for the presence of a cancer, including adenocarcinomas (see page 2, paragraphs 1-3), the new grounds of rejection above addresses this issue using the Sorenson reference.

7. With regard to the rejections of claims 5, 7, 9, 12, 19, 23 and 29 under 35 USC 103(a), Applicants' arguments are found persuasive and the rejections are withdrawn herein in view of persuasive arguments and new grounds of rejections.

8. With regard to the obviousness-type double patenting rejections, Applicants' arguments are fully considered and the rejections are maintained herein until a terminal disclaimer is submitted.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M , Mon - Friday,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Suryaprabha Chunduru
Primary Examiner
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Prabha Chunduru
SURYAPRABHA CHUNDURU
PATENT EXAMINER
11/9/06